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Ototoxicity in Children With Malignant Brain Tumors Treated With the "8 in 1" Chemotherapy Protocol

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Background. Adjuvant chemotherapy has improved the outcome of childhood malignant brain tumors in large randomized trials. With increasing survival rates, treatment toxicity has become a matter of concern. Radiation therapy and cisplatinum are known to be ototoxic.

Methods. We evaluated the incidence and factors predisposing to ototoxicity in children treated with the "8 in 1" chemotherapy protocol in Finland during 1986–1993. Thirty-five of the 82 children survived for at least 1 year after diagnosis. Thirty of these children were old enough to have an audiogram.

Results. Seventeen of the 30 children had normal hearing, seven had hearing loss at high frequencies, and six (20%) had severe hearing loss in the speech range. The risk factors for severe hearing loss were young age, a high cumulative dose of cisplatinum, and deteriorating renal function. In the presence of these factors, the risk of severe hearing loss was over 50%. Hearing loss at high frequencies could occur after low cumulative doses of cisplatinum, but severe hearing loss correlated with high cumulative doses.

Conclusions. Cisplatinum-induced hearing loss at high frequencies is common, but hearing loss in the speech range also occurs, particularly in children with predisposing factors, and may progress insidiously and rapidly. Therefore a hearing test before each "8 in 1" course is important.

Key words: "8 in 1" chemotherapy, cisplatinum, ototoxicity

INTRODUCTION

Adjuvant chemotherapy has proved to be beneficial in the treatment of childhood brain tumors in large randomized trials, especially for medulloblastoma and primitive neuroectodermal tumor (PNET) [1,2]. With increasing survival rates, the long-term toxic effects of treatment become more important.

Bleyer introduced the "eight drugs in one day" chemotherapy protocol in 1983 [3]. Seven cytostatic drugs, including cisplatinum, vincristine, CCNU, procarbazine, hydroxyurea, cytosine arabinoside, dacarbazine or cyclophosphamide plus methylprednisolone, are administered within 12 hours, and the treatment is repeated ten times at 6-week intervals during 1 year. Radiotherapy is given after the first two courses of treatment. Each of the chemotherapeutic agents is efficacious when given alone [4], but the combined use of multiple agents circumvents drug resistance [5]. The drugs are administered in a sequence which takes advantage of the known synergistic or additive anti-neoplastic mechanisms. A short exposure of the bone marrow to multiple drugs is known to be less myelosuppressive [6].

The cornerstone of the "8 in 1" chemotherapy is cisplatinum. The adverse effects of cisplatinum include nausea, vomiting, myelosuppression, nephrotoxicity, neurotoxicity, and ototoxicity [7]. The hearing loss is normally symmetrical and irreversible, and affects high sound frequencies. With increasing cumulative doses, the ototoxicity may be progressive [8–13]. The risk of ototoxic injury is further increased by a rapid cisplatinum infusion, subsequent use of other ototoxic drugs, a pre-existing hearing loss, and dehydration [8,12]. Cranial irradiation alone does not usually cause major hearing loss, but may have an additive effect with chemotherapy [8].

The hearing loss associated with cisplatinum, radiation therapy, or brain tumors themselves has been evalu-

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TABLE I. Clinical Data for the 35 Patients Who Were Treated With "8 in 1" Chemotherapy and Survived at Least 1 Year After Diagnosis

Mean age at diagnosis, (range, years)	5.3 (0.1–14.7)
Sex (m/f)	22/13
Histology	
PNET/medulloblastoma	20
High-grade ependymoma	4
High-grade astrocytoma	3
Others	8
Site of tumor	
Hemisphere/midline/posterior fossa	14/3/18
Resection	
Grossly total/partial/biopsy	15/19/1
Shunted hydrocephalus	19
Volume of radiotherapy	
None/local/cranial/craniospinal	3/8/3/21
Mean doses of radiotherapy (cGy)	
For tumor/whole brain/spine	4,730/3,410/3,100
Mean fraction (range, cGy)	170 (120–200)
Number of "8 in 1" courses	
1–7/8–10	6/29
Cumulative dose of cisplatinum	
(Mean, range, mg/m^2)	548 (180–900)

ated in different settings [8,9,12]. The incidence is not exactly known and the risk of severe hearing loss is difficult to predict in an individual. We have treated 82 children with malignant brain tumors with "8 in 1" chemotherapy during 1986–1993 in Finland. The purpose of our study was to evaluate the incidence and severity of ototoxicity in this uniformly treated group of 35 patients surviving for at least 1 year after diagnosis, with special emphasis on risk factors predisposing to severe hearing loss.

PATIENTS AND METHODS

Patients

Our original study group initially comprised all 82 children aged 0.1–16.8 years, 49 males and 33 females, who were treated for brain tumors with the "8 in 1" chemotherapy protocol in Finland during 1986–1993. The 5-year survival rate for malignant brain tumors as a whole was 43% and separately 63% for medulloblastomas, 27% for high-grade astrocytomas, and 0% for brainstem tumors [14]. The characteristics of 35 patients, who survived for at least 1 year after diagnosis, are presented in Table I. There were 20 medulloblastomas or primitive neuroectodermal tumors (PNET), four high-grade ependymomas, three high-grade astrocytomas, and eight other tumors. Thirty-two children were treated with radiotherapy, and 24 received whole brain irradiation. Local radiotherapy (boost) was delivered through two opposite lateral open or wedged fields. Twenty-nine patients received at least eight courses of the "8 in 1" therapy. The mean cumulative dose of cisplatinum was 548 mg/m^2.

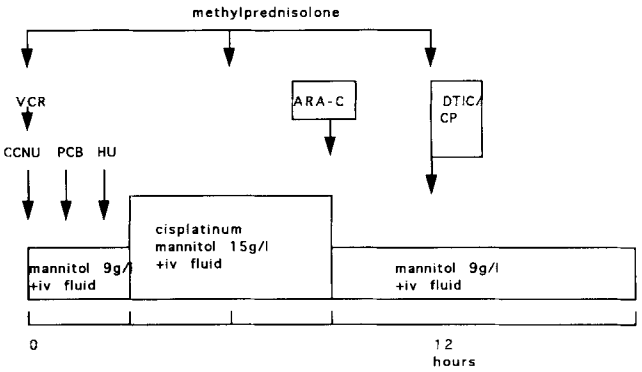

Fig. 1. Time schedule of an "8 in 1" chemotherapy course.

The schedule for the "8 in 1" chemotherapy is shown in Figure 1. Patients with medulloblastoma or PNET were treated according to regimen B, which included cyclophosphamide. Patients with gliomas or ependymomas were treated with regimen A, which included dacarbazine (DTIC). The doses of hydroxyurea and cisplatinum were higher in regimen A. Cisplatinum of 60 or 90 mg/m^2 was delivered in half-normal saline (3,000 ml/m^2/day) with mannitol (15 g/l) over 6 hours.

Methods

The radiation dose to the inner ear (which received the larger dose) was evaluated from simulation films, isodose curves, and radiotherapy records. If the inner ear was within the treatment volume, the dose was defined as equal to the target dose. In other cases the dose was considered negligible.

Of the 35 surviving children, 30 have had an audiogram after the "8 in 1" treatment. The middle ear status was checked to exclude otitis media at the time the audiogram was obtained. Five children were too young or disabled to co-operate. The mean interval between radiotherapy and the last audiogram was 2.7 years (range 0.6–6.3 years). The better ear was evaluated at frequencies of 500, 1,000, 2,000, 4,000, 6,000, and 8,000 Hz. A hearing loss greater than 25 dB was considered significant. We used the dB ISO standard.

Glomerular filtration rate (GFR) was evaluated by Cr-EDTA or creatinine clearance during the "8 in 1" treatment period. Corrected for differences in body surface area, it reaches adult maturity by 2 years of age [15]. The mean lowest value of renal GFR during the "8 in 1" treatment was 1.1 ml/s/1.73 m^2 (range 0.5–1.8) in children over 2 years of age. GFR decreased below 1.0 ml/s/1.73 m^2 in 9/21 children (43%), and the doses of cisplatinum had to be reduced in 7/35 children.

Statistical Methods

Student's t-test and the Chi-square test were used for the statistical analyses.

TABLE II. Results of the Last Audiogram in the Better Ear Compared to Predisposing Factors for Severe Hearing Loss (n = 30)

Hearing loss	None or mild 4,000–8,000 Hz	Severe 500–2,000 Hz	
Normal, threshold <25dB	17		
4,000–8,000 Hz/>25dB	7		
500–2,000 Hz/>25dB		6	
Total	24 (80%)	6 (20%)	
Age (mean, years)	6.8	3.1	$P = 0.04$
Male/female	15/19	3/3	
Site of tumors			
Hemisphere	10	1	
Midline	1	2	
Post. fossa	13	3	$P = 0.09$
Cumulative dose of cisplatinum			
Mean, mg/m^2	510	690	$P = 0.04$
Renal impairment			
GFR in children over 2 years of age (Pt-EDTA or creatinine clearance)			
Mean, ml/s/1.73 m^2	1.2 (n = 15)	0.7 (n = 5)	$P = 0.01$
Doses of irradiation to the inner ear			
Mean, cGy	3,700 (n = 24)	4,360 (n = 6)	$P = 0.37$
Fractions			
Mean, cGy	176	160	

RESULTS

Thirty children survived for at least 1 year after diagnosis and were old enough to co-operate in audiogram testing. Seventeen of them (57%) had normal hearing at 25 dB threshold, seven (23%) had hearing loss at high frequencies (4,000–8,000 Hz), and six (20%) had severe hearing loss in the speech range (500–2,000 Hz) (Table II). Figure 2 illustrates the typical progression of hearing loss at high frequencies in one patient and Figure 3 the progression of severe hearing loss in the speech range with increasing cumulative doses of cisplatinum in another patient. Hearing loss at high frequencies occurred early even with a low cumulative dose of cisplatinum, but severe hearing loss in the speech range usually occurred only after high cumulative doses (Figs. 4 and 5).

We evaluated predisposing factors by comparing the children with normal hearing or insignificant hearing loss at high frequencies with those who had hearing loss in the speech range (Table II). The mean ages were 6.8 vs. 3.1 years ($P = 0.04$). The mean cumulative dose of cisplatinum was 510 vs. 690 mg/m^2 ($P = 0.04$). The lowest value for the glomerular filtration rate (GFR, Cr-EDTA- or creatinine clearance) in children over 2 years of age was 1.2 vs. 0.7 ml/s/1.73 m^2 ($P = 0.01$). Irradiation doses in the inner ear were 3,700 vs. 4,360 cGy ($P = 0.37$). Of the tumor sites, 10 vs. 1 were located in a cerebral hemisphere, 1 vs. 2 in the midline around the third ventricle, and 13 vs. 3 in the cerebellum ($P = 0.09$), respectively. The risk factors that reached statistical significance were age at the time of diagnosis, the cumulative dose of cisplatinum, and deterioration of renal function (Table II). The material was too small to allow statistical conclusions about interactions or independence of these risk factors.

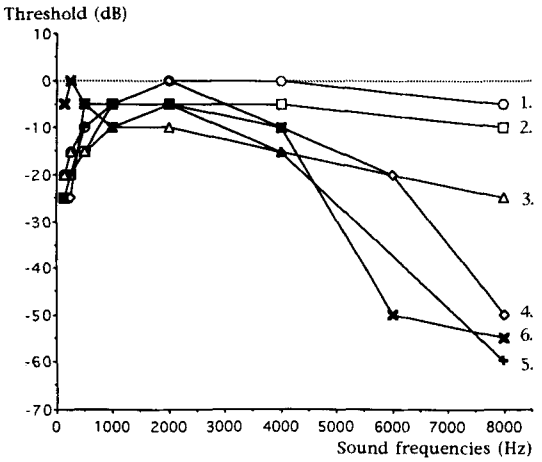

Fig. 2. Typical progression of hearing loss after increasing cumulative doses of cisplatinum in one patient. The numbers indicate audiograms performed after successive cumulative doses of cisplatinum (mg/m^2) and increasing time after diagnosis (years) as follows: ○, 270/0.4; □, 450/0.6; △, 630/0.8; ◇, 810/1.1; +, 900/1.2; ×, 900/5.2.

Table III compares the increasing incidence of severe hearing loss to the presence of different risk factors in this series. With several predisposing factors, the risk of developing severe hearing loss is substantial (over 50%).

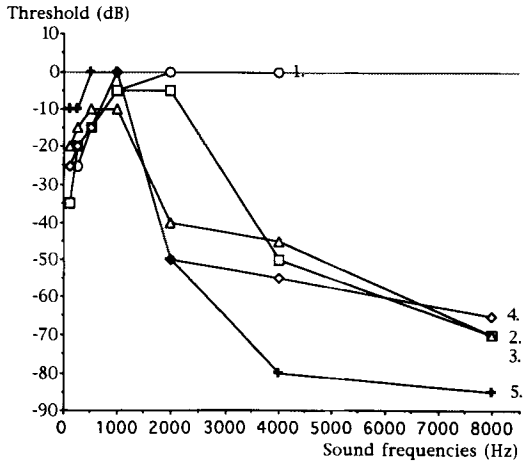

Fig. 3. Progression of severe hearing loss in the speech range in a single patient. The numbers indicate audiograms performed after successive cumulative doses of cisplatinum (mg/m^2) and increasing time after diagnosis (years) as follows: ○, 450/0.7; □, 540/0.8; △, 720/0.9; ◇, 900/1.1; +, 900/5.1.

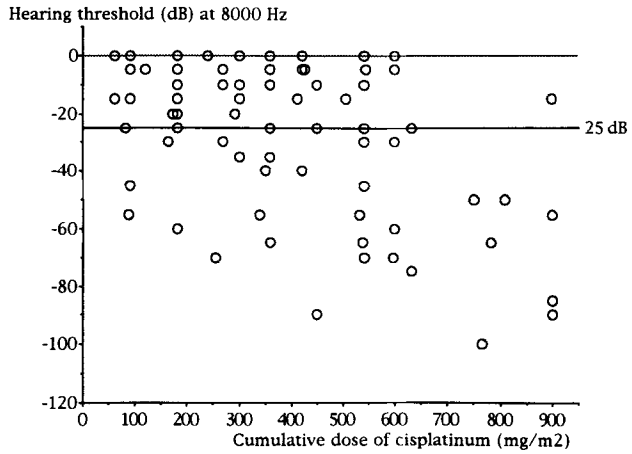

Fig. 4. Correlation between the cumulative dose of cisplatinum and the hearing threshold at 8,000 Hz, indicating that hearing loss at high frequencies may occur early even after low cumulative doses of cisplatinum. The symbols indicate individual measurements (1–7 per child).

All six children with severe hearing loss in the speech range were less than 5 years of age at the time of diagnosis and four were less than 3 years. In five of them, the tumors were located in the midline around the third ventricle or in the posterior fossa. Four children had a glioma and five were treated on regiment A including cisplatinum of 90 mg/m^2 per course. The mean cumulative dose of cisplatinum was 689 mg /m^2 (range, 425–900 mg/m^2). All developed renal insufficiency and in three the dose of cisplatinum had to be reduced. Three children use hearing aids (Table IV).

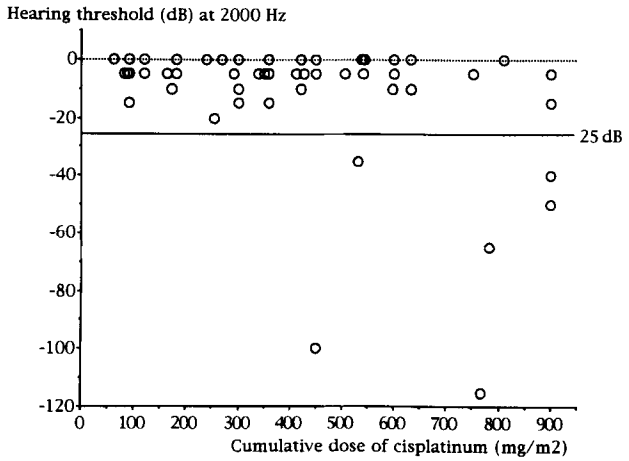

Fig. 5. A correlation between the cumulative dose of cisplatinum and the hearing threshold at 2,000 Hz, indicating that severe hearing loss in the speech range usually occurs after higher cumulative doses of cisplatinum.

DISCUSSION

Hearing loss is common in children with malignant brain tumors treated with radiotherapy and cisplatinum. In our study, a hearing loss at high frequencies occurred in 23% (n = 7) and a severe hearing loss in the speech range in 20% (n = 6). Three children required hearing aids. In a study by Schell, 177 children with various malignant neoplasms were tested for hearing loss after a mean cisplatinum cumulative dose of 407 mg/m^2. Hearing loss in the speech range was noted in 11% and about half of the patients had substantial hearing deficits at high frequencies [9]. In Kretschmar's study, a preradiation cisplatinum dose of 300 mg/m^2 resulted in a clinically significant hearing loss at frequencies of 2,000 Hz or lower in 11% of the children [8].

A high cumulative dose of cisplatinum has been reported as a risk factor for hearing loss [9,12]. In our study, hearing loss at high frequencies occurred early even after low cumulative doses of cisplatinum (Fig. 4) in some children, but severe hearing loss in the speech range occurred only after higher cumulative doses (Fig. 5). Although the expected hearing loss at high frequencies has little effect on speech, hearing threshold shifts at high frequencies are warning signs for subsequent shifts at low frequencies. Our findings are in agreement with the results of Schell et al., who found a 50% increase in hearing loss at high sound frequencies after cisplatinum doses below 360 mg/m^2. If the cisplatinum dose was increased from 450 to 750 mg/m^2, nearly a third of their patients developed a hearing loss in the speech range [9].

The risk of significant hearing loss is difficult to predict at the individual level. Children less than 5 years of age with severe renal insufficiency are at greatest risk.

TABLE III. Increasing Incidence of Severe Hearing Loss in the Speech Range With Different Predisposing Factors

Predisposing factors	Incidence (%)	Number of patients
All patients	20	6/30
Cumulative dose of cisplatinum		
>400 mg/m^2	25	6/24
>600	33	4/12
>800	50	2/4
Age at diagnosis		
<7 years	33	6/18
<5	37	6/16
<3	50	4/8
GFR in over 2-year-old children		
<1.4 ml/s/1.73 m^2	31	5/16
<1.2	41	5/13
<1.0	44	4/9
<0.8	75	3/4
Cumulative dose of cisplatinum >600 mg/m^2		
Plus irradiation dose for the inner ear >3500 cGy	33	4/12
Plus age at diagnosis <5 years	57	4/7
Plus GFR <1.2 ml/s/1.73 m^2	80	4/5

TABLE IV. Clinical Data on the Six Children With Severe Hearing Loss in the Speech Range*

Age at dg (yrs)	Site of tumor	Xt volume dose (cGy) in inner ear	Cisplatinum cumulative dose (mg/m^2)	GFR lowest value (ml/s/1.73 m^2)	Audiogram lowest frequency threshold	Hearing aid
1.8 PNET	Left temporal lobe	Crsp 3,620	425 reduced	0.6	2,000 Hz/60 dB	No
2.0 Glioma	Post fossa IV ventr. infiltrating brain stem	Cr 4,000	765	0.6	500 Hz/65 dB	Yes
2.2 Medulloblastoma	Cerebellum	Crsp 4,800	900	1.08	2,000 Hz/40 dB	No
2.7 Ependymoma	Post fossa IV ventr.	Crsp 4,800	810	0.82	2,000 Hz/50 dB	Yes
4.7 Glioma	Midline near the thalamus	Cr 4,260	783 reduced	0.6	1,000 Hz/30 dB	Yes
4.9 Glioma	Midline supracellar	Local 4,700	450 reduced	(?) renal injury	1,000 Hz/40 dB	No

*Cr = cranial; Crsp = craniospinal; GFR = glomerular filtration rate; Xt = irradiation.

Schell et al. also detected three risk factors: young age, prior irradiation, and the presence of a CNS neoplasm [9]. The fact that severe hearing loss tends to occur in young children is a serious problem. Children less than 3 years of age cannot be tested reliably with conventional audiograms and the hearing loss typically develops insidiously. Appropriate, reliable tests for these very young children would include visual reinforcement audiometry, auditory brainstem response testing, and otoacoustic emissions testing. These special tests are not available in all centres treating children with brain tumors, and are not routinely used. All our children with severe hearing loss had simultaneous renal insufficiency. Pollera et al. found a relationship between acute hearing loss and an increase of serum creatinine level [11], which could indicate that the inner ear and kidney are equally susceptible to cisplatinum toxicity; on the other hand, renal insufficiency may also have increased the toxicity of cisplatinum through delayed renal clearance.

Prior or simultaneous irradiation of the inner ear area is probably an additive risk factor for severe hearing loss [8,9]. In our study, we were unable to establish irradiation as a significant predisposing factor, possibly because the doses to the inner ear were uniformly high, and the number of patients was small. In Schell's study, prior cranial radiation therapy increased hearing loss by 20 to 30 dB [9]. It has been suggested that the sensitivity of the cochlea to cisplatinum may be increased by postirradiation hyperemia. In Kretschmar's study, radiation therapy did not increase the ototoxicity of cisplatinum when the drug was given before, as opposed to after cranial irradiation [8]. The timing of cisplatinum in relation to cranial irradiation may thus be of significance.

In conclusion, cisplatinum causes hearing loss in children with brain tumors, most commonly at high sound frequencies. Hearing loss in the speech range is less common, but tends to occur particularly in young children with simultaneous renal impairment after high cumulative doses of cisplatinum. In very young children, hearing loss may be particularly harmful for subsequent speech development and should therefore be monitored closely. Because progression of hearing loss may be

rapid and insidious, children with predisposing factors should have hearing tests performed before each "8 in 1" or other cisplatinum-including course.

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